Symposium Anouncement

September 22nd 2014, Department of Toxicology, University of Wuerzburg, Germany

Bioactivation of Xenobiotics and Covalent Binding to Proteins: Implications for Target-Organ Toxicity

in Honour of Prof. Dr. Wolfgang Dekant's 60th birthday

Organizers

Julius-Maximilians-
UNIVERSITÄT WÜRZBURG
Department of Pharmacology and Toxicology

Department of Pharmacology and Physiology
UNIVERSITY of ROCHESTER MEDICAL CENTER

Program

9:00 – 10:00	Get Together
10:00 – 10:20	*Welcome address.* Prof. Dr. M.W. Anders, Chair, University of Rochester, NY, USA
10:20 – 11:00	*Global Analysis of Lipid Electrophile Protein Adducts and Redox Modifications.* Prof. Dr. Dan Liebler, Vanderbilt University, Nashville, TN, USA
11:00 – 11:40	Coffee break
11:40 – 12:20	*Molecular and Cellular Consequences of Covalent Target Protein Modification.* PD Dr. Angela Mally, University of Wuerzburg, Germany
12:20 – 13:00	*Mapping Cellular Signaling Networks Controlling Stress Response Pathways in Adverse Drug Reactions.* Prof. Dr. Bob van de Water, Leiden University, The Netherlands
13:00 – 14:00	Lunch
14:00 – 14:40	*Biotransformation, Reactive Intermediates, and Covalent Binding: Two Faces of Glutathione S-Conjugate Formation.* Prof. Dr. Wolfgang Dekant, University of Wuerzburg, Germany
14:40 – 15:20	*In silico/Computational Prediction of Reactive Intermediates: Structural Alerts (Toxicophore), Structure-Toxicity Relationships, Pathways of Reactive Intermediates Formation.* Dr. Alexander Amberg, Sanofi-Aventis Deutschland GmbH, Frankfurt am Main
15:20 – 16:00	Coffee break
16:00 – 16:40	*Hepatocyte Models for Reactive Metabolites and Toxicity Prediction.* Prof. Dr. Stefan O. Müller, Merck KGaA Darmstadt, Germany
16:40 – 17:30	Overall discussion and conclusions
17:30	Reception
19:00	Dinner

The bioactivation of drugs chemicals to chemically reactive intermediates and their covalent binding to proteins is widely implicated in chemical toxicity.

Target-organ toxicity is often the consequence of the covalent binding of reactive metabolites to protein targets, but relevance of specific protein targets and the downstream mechanisms that finally result in organ damage or failure has not been defined. Although many protein targets for reactive drug metabolites have been identified, the role of covalent binding in toxicity is difficult to generalize since covalent binding may lack apparent toxic consequences or may be associated with major organ damage. Although the covalent binding of reactive intermediates generated by biotransformation of drugs or chemicals is a key initial event in chemical-induced toxicity, the biological mechanisms by which the covalent modification of proteins induces cell damage and death are still poorly understood.

Low-incidence, drug-induced organ toxicity is a major cause of market withdrawals of approved drugs. Such low-incidence effects ("idiosyncratic" toxicities) are difficult to predict in preclinical toxicity screening, and the role of covalent binding in low-incidence drug toxicity is not well defined. Although the downstream events that follow bioactivation to a reactive metabolite are poorly understood, target-organ toxicity, specifically liver toxicity, is often associated with the bioactivation of a drug or chemical to a reactive electrophilic metabolite.

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